II. REMARKS

The final Office Action dated August 5, 2009, has been received and carefully noted. The above amendments and the following remarks are being submitted as a full and complete response thereto. Applicant respectfully requests reconsideration and withdrawal of the rejections.

Claims 1-9 are pending in this application. Claims 2, 5, and 6 are withdrawn. By this Amendment, claims 1, 7, and 8 are amended. Support for the amendments may be found in the specification and claims as originally filed. Applicant submits that no new matter is added.

Entry of this Amendment is proper under 37 C.F.R. §1.116 since this Amendment: (a) places the application in condition for allowance for reasons discussed herein; (b) does not raise any new issue regarding further search and/or consideration since the Amendment amplifies issues previously discussed throughout prosecution; (c) does not present any additional claims without canceling a corresponding number of finally-rejected claims; and (d) places the application in better form for appeal, should an appeal be necessary. Entry of the Amendment is thus respectfully requested.

Claims 1, 3, 4, and 7-9 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. This rejection is traversed.

As acknowledged by the Examiner, "the specification reasonably conveys to one skilled in the relevant art that the genus of 'pharmaceutically acceptable salts' is described . . ." (final Office Action, page 7). See also, for example, the support for the above claim amendments at page 24, paragraphs 2-3 of the originally filed specification.

Accordingly, in view of the above amendments to claims 1, 7, and 8, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 1, 3, 4, and 7-9 under 35 U.S.C. § 112, first paragraph.

Claims 1, 3, 4, 7, and 8 are rejected under 35 U.S.C. §103(a) as being unpatentable over Armour et al. (Arthritis and Rheumatism, 44(9):2185-92 (2001)) in view of Jang et al. (Free Radical Biology & Medicine, 24(9):1511-19 (1998)). Applicant respectfully traverses this rejection.

Applicant agrees with the Examiner that "Armour et al. does not specifically teach the method of treating degeneration of the cartilaginoid matrix comprising administering to a subject in need thereof an effective amount of one or more compounds or salts thereof having the formula (I), or the elected species (instant claim 1)" (final Office Action, page 9). Further, Applicant respectfully submits that Jang et al. does not fulfill this deficiency of Armour et al., as Jang et al. does not teach or suggest the use of the presently claimed compounds to treat degeneration of the cartilaginoid matrix.

In fact, Jang et al. teaches away from utilizing the NO-compounds of Armour et al. to treat degeneration of the cartilaginoid matrix. For example, Jang et al. discloses that "NO has limited modulating effects in cartilage metabolism, with evidence for both protective and deleterious effects" (Jang et al., Abstract). Further, as noted by the Examiner, "Jang et al. teaches both NO from chondrocytes can lead to both matrix degradation . . ., as well as PGE_2 leading to inflammation and matrix degradation (page 1515, Fig. 1 at top of page)" (final Office Action, page 9). While Jang et al. discloses that "data also exist to suggest that NO is protective, at least for the cartilage matrix," Jang et al. notes the mounting evidence for NO in catabolic events and merely

concludes that "inhibition of NO synthase may not necessarily be beneficial in preventing cartilage breakdown" (Jang et al., page 1517, paragraph bridging the left and right column). As such, a person of ordinary skill in the art would not have been motivated to administer additional NO via a NO-compound to an arthritic patient, much less to treat degeneration of the cartilaginoid matrix.

Further, Applicant notes that Jang et al. is directed to the role of endogenous nitric oxide (NO) in arthritis (i.e., the role of NO produced inside the body and regulation of such NO by the inhibition or activation of specific enzymes). The presently claimed invention discloses compounds which may provide exogenous NO in the body in addition to endogenous NO.

NO in cells is synthesized by a family of enzymes termed the nitric oxide synthases (Jang et al., paragraph bridging pages 1511 and 1512). In addition to two constitutive NO synthases, an inducible NO synthase (i-NOS, NOS II), typically not present in cells, can be expressed in response to cytokines (Jang et al., page 1512, right column, second full paragraph). Blood mononuclear cells of patients with rheumatoid arthritis were found to express iNOS (Jang et al., page 1512, right column, lines 1-3). As such, the inhibition of iNOS decreases the level of endogenous NO. Jang et al. discloses that "[a]dministration of NO synthase inhibitors suppressed the development of arthritis," particularly in inflammatory arthritis model (Jang et al., page 1514, left column, second full paragraph). As such, Jang et al. teaches that decreasing the level of NO suppresses arthritis development.

In addition to the negative effects of endogenous NO on arthritis, Jang et al. evaluated whether the inhibition of NO synthase (i.e., decreasing endogenous NO) may

be beneficial in preventing cartilage breakdown and concluded that that a definitive role of NO (endogenous) in arthritis remains elusive in view of its "conflicting actions" (Jang et al., page 1517, paragraph bridging the left and right columns).

Further, Applicant respectfully submits that one of ordinary skill in the art would not have been motivated to combine Armour et al. and Jang et al., much less to obtain the presently claimed invention. By reading the fourth full paragraph in the right column on page 1516 of Jang et al. in its entirety, it is clear that Jang et al. discloses that decreasing the intracellular production of PGE_2 and NO in a combination therapy may be beneficial. Further, Jang et al. discloses that "NO has adverse consequences in inflammation" and that "aspirin-like inhibitors of COX [where COX is an enzyme that produces PGE_2] are able to inhibit iNOS [enzyme producing NO]." As Jang et al. teaches targeting NO and PGE_2 to decrease the intracellular production of both species, Jang et al. clearly teaches away from the use of a NO donor, such as the compounds of Armour et al.

For at least the above reasons, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 1, 3, 4, 7, and 8 under 35 U.S.C. §103(a) over Armour et al. in view of Jang et al.

Claim 9 is rejected under 35 U.S.C. §103(a) as being unpatentable over Armour et al. in view of Jang et al. as applied to claims 1, 3, 4, 7, and 8 above, and further in view of Gabalawy et al. (Arthritis Res. 4(suppl 3):S297-301 (May 9, 2002)). Applicant respectfully traverses this rejection.

Applicant agrees with the Examiner that "Armour et al. in view of Jang et al. does not specifically disclose the method wherein relapses of degeneration of the cartilaginoid matrix are reduced" (final Office Action, page 12).

Further to the remarks above, Applicant submits that El-Gabalawy et al. does not satisfy the above-discussed deficiencies of Armour et al. and Jang et al., as El-Gabalawy et al. does not teach or suggest the use of the presently claimed compounds to treat degeneration of the cartilaginoid matrix.

For at least the above reasons, Applicant respectfully requests reconsideration and withdrawal of the rejection of claim 9 under 35 U.S.C. §103(a) over Armour et al. in view of Jang et al., and further in view of Gabalawy et al.

III. CONCLUSION

Applicant respectfully submits that this application is in condition for allowance and such action is earnestly solicited. If the Examiner believes that anything further is desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact Applicant's undersigned representative at the telephone number listed below to schedule a personal or telephone interview to discuss any remaining issues.

In the event that this paper is not being timely filed, the Applicant respectfully petitions for an appropriate extension of time. Any fees for such an extension, together with any additional fees that may be due with respect to this paper, may be charged to Counsel's Deposit Account Number 01-2300, referencing Docket Number **026220-00055**.

Respectfully submitted,

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